Immunodiagnosis in parasitic disease

SIR,—Drs J K Cruickshank and C Mackenzie in their leading article (21 November, p 1349) rightly draw attention to the promising prospects opened up by the introduction of the enzyme-linked immunosorbent assay (ELISA) technique and of monoclonal antibodies. We agree with this, yet think that a more critical approach is needed.

The specificity required for diagnostic tests is high. In a series with 5% true positives, an additional 1% of false positives would mean that one in six of all positives were false. Parasites are masters at antigenic disguise, either by mimicry or incorporation of host antigens. False-positives, therefore, are as likely to occur in diseases which cause the release of tissue antibodies as in patients with other parasitic diseases; yet in many evaluations of immunodiagnostic tests the controls are drawn only from the last group or from blood donors. Not surprisingly, in clinical practice the results may be less good than the claims. General hospital patients need to be included among the controls.

The advantages of ELISA are its suitability for mass screening and the lack of subjectivity in interpretation. As regards parasitology, the former characteristic is of value for seroepidemiology but not as yet for serodiagnosis, which is almost always done on a small scale. The method has no inherent advantages as regards specificity; and unless purified antigen is available it may be less specific than, for instance, immunofluorescence, in which cross-reactive structures in a parasite can be disregarded. In this department we find that even purified parasite antigens can give false-positives in conditions where, for example, there is liver damage.

Nevertheless, purified antigens, if they were freely available, would be a great advance. Who is to provide them? Over and over again commercial firms have produced satisfactory parasite antigens; but many have not been made universally available, or else after a short time they have been withdrawn. To many people the obvious agency would appear to be the World Health Organisation, which could ensure international standardisation and offer the products at a price which the Third World could afford. However, except in isolated instances WHO has not so far seen this to be its role.

These and other aspects of the subject are dealt with more fully in recent reviews.[1 2] The hopes which your editorial raises are more likely to be realised if the problems are faced.

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Malaria

SIR,—We were very interested in Professor H M Gilles' article on malaria (21 November, p 1382), having in the past month experienced some difficulty in diagnosing a case of vivax malaria. We feel that Professor Gilles does not emphasise enough the occasionally very prolonged latency of vivax malaria. Nor does he mention the use of bone-marrow aspiration in aiding diagnosis when parasites are not seen on peripheral blood films.[1] We would like to illustrate the importance of both these points in the following case report.

A previously well 37-year-old farmer's daughter, who works as a caterer, presented with a 10-day history of diarrhoea, vomiting, and headache and on examination was found to have a temperature of 40·3°C and tender splenomegaly of 3 cm. She denied any foreign travel for over two years. The diagnosis remained elusive for over a week despite repeated blood films, which only showed her to be increasingly pancytopenic; finally haemoglobin was 8·1 g/dl, white cell count $2{\cdot}2 \times 10^9$/l, and platelets $69{\cdot}0 \times 10^9$/l. She had a weakly positive monospot, antinuclear factor, and smooth-muscle antibodies, together with a bilirubin of 35 μmol/l (normal up to 19 μmol/l). She deteriorated, with increasing splenomegaly, and had rigors every other day. The patient had by now recalled her three-month trekking holiday in west Africa, exactly 34 months before, during which she had taken weekly chemoprophylaxis that unfortunately she had discontinued on return after two weeks. She had had no previous symptoms. Thick films were examined without a result and therefore on the eighth day of hospital stay a bone marrow aspiration was performed which showed schizonts of *Plasmodium vivax*. Retrospective examination of blood films did show occasional parasites.

The incubation of *P vivax* can be up to nine months and relapses may occur for up to eight years. Occasionally, first attacks may be occult owing to insufficient chemoprophylaxis, which may also prolong the incubation period.[2] The above case demonstrates the importance of a full travel history and also the use of bone-marrow aspiration in making a diagnosis in a pyrexia of unknown origin.

We would like to thank Drs M J O'Shea and N Mitchell for all their help in making the diagnosis.

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Pathogenesis and treatment of myasthenia gravis

SIR,—A few comments on the review "Pathogenesis and treatment of myasthenia gravis" by Professor Scadding and Dr Harvard (17 October, p 1008) are in order. On the basis of 30 years' experience and observation of 2100 myasthenic patients we agree with many of the author's comments, but take issue with others.

(1) Extraocular spread one year after onset of ocular symptoms is not rare. Grob recently pointed out that about 20% of such patients' symptoms may progress even after two years of clinical stability.[1]

(2) While the occurrence of germinal centres is relatively rare after the age of 40, serum acetylcholine receptor antibody titres in severe generalised myasthenia gravis have not, in our experience, been in the "lowest range" in this age group.

(3) Over 50% of our purely ocular patients have normal values for acetylcholine receptor antibody and less than a third of these patients respond to steroids.[2] Furthermore, we do not feel that steroid therapy should be used routinely for prolonged periods of time in anticholinesterase-resistant myasthenic patients. With the risks attendant on steroid therapy in general, there is some question about whether ocular myasthenia gravis should at any time be treated with steroids.

(4) While 12% was the generally accepted rate of incidence of neonatal myasthenia gravis in non-thymectomised mothers, this incidence is appreciably lower in the pregnancies of thymectomised mothers.

(5) We have previously shown that striated muscle antibodies, probably not pathogenic in myasthenia gravis, have roughly the same distribution as acetylcholine receptor antibodies—for example, low incidence in ocular myasthenia gravis, high in severe generalised myasthenia gravis, and almost universally elevated in thymomas.[2 3]

(6) Pyridostigmine can indeed be given parenterally and is available from Hoffman-LaRoche in concentrations of 5 mg/ml. The oral:parenteral pyridostigmine dose ratio is about 30:1.

(7) We have not been impressed with the results of azathioprine therapy (2·5-3·0 mg/kg/day) given in conjunction with plasmapheresis therapy in 12 patients over a three-year period. In no instance was the azathioprine able to abolish the need for periodic plasma exchange, although the intervals between treatments could be prolonged in eight out of 12 patients.

(8) The need for total removal of all thymic tissue in myasthenia gravis remains unproved. Furthermore, considerable doubt exists whether total thymectomy via any surgical approach is even possible.

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Postexposure immunoprophylaxis against B virus infection

SIR,—Dr E A Boulter and his colleagues (5 December, p 1495) suggest that people bitten by monkeys latently infected with simian herpesvirus (B virus) should be given specific monkey antiserum topically by injection. They admit that one patient who was given this material in a phalanx had severe pain the following night.

Monkey bites and monkey scratches are quite common in an institution such as the University of Oxford with a large number of monkeys kept for experimental purposes. A fair proportion of them are seropositive. I find it surprising that the authors did not suggest the far more logical and certainly far less painful approach of using topical acyclovir, which when dissolved in dimethylsulphoxide penetrates the skin and causes the sufferer comparatively little discomfort. Boulter and colleagues[1] showed that acyclovir was effective in the treatment of experimental B virus infection in rabbits. It is reasonable to assume that it will also work in human beings.

It is difficult enough as it is to persuade people who have been bitten by monkeys to come and have swabs taken and have their cuts, bites, and scratches dealt with. This may happen about 20 times a year in a large